

Combination Therapy of HBV Peginterferon and Nucleosides/Nucleotides

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No single drug, used in monotherapy, has a satisfactory long-term efficacy in the treatment of chronic hepatitis B. The future of chronic hepatitis B therapy seems to be in the combination of different drugs. Ideally, the optimal drugs to combine would meet the following criteria: they should have different mechanisms with effective immunomodulation and a potent antiviral effect, an excellent safety and resistance profile, and they should induce a sustained response with a limited duration of therapy. So far, the combination of two nucleoside/nucleotide analogues has not shown superiority as compared with one analogue alone. Only the combination of pegylated interferon (PEG IFN) with lamivudine has been well studied. Three randomized controlled trials (two in HBeAg-positive and one in HBeAg-negative chronic hepatitis B) assessed the efficacy and safety of the combination of PEG IFN with lamivudine.

HBeAg-Positive Chronic Hepatitis B

In a controlled trial, 307 patients were randomized to receive either the combination of PEG IFN alpha 2b and lamivudine or PEG IFN alpha 2b with placebo.¹ At the end of treatment, 51% and 34% had normal ALT; 33% and 10% had undetectable HBV DNA; and 25% and 22% had HBe seroconversion. Six months post-treatment, 35% and 36% had normal ALT; 9% and 7% had undetectable HBV DNA; 29% and 29% had HBe seroconversion; and 7% and 5% had HBs seroconversion in the combination and the monotherapy arms, respectively.

In another controlled trial, 814 patients were randomized to receive either the combination of PEG IFN alpha 2a and lamivudine or PEG IFN alpha 2a with placebo or lamivudine alone.² At the end of treatment, mean decrease in HBV DNA was 7.2, 4.5, and 5.8 log copies per mL; 46%, 39%, and 62% had normal ALT; 69%, 25%, and 40% had undetectable HBV DNA; and 24%, 27%, and 20% had HBe seroconversion. Six months post-treatment, 39%, 41%, and 28% had normal ALT; 14%, 14%, and 5% had undetectable HBV DNA; 27%, 32%, and 19% had HBe seroconversion; and 3%, 3%, and 0% had HBs seroconversion in the combination, the PEG IFN monotherapy, and the lamivudine monotherapy arms, respectively. Rates of resistance to lamivudine were 4% and 27% in the combination and the lamivudine monotherapy arms, respectively.

HBeAg-Negative Chronic Hepatitis B

In one controlled trial, 537 patients were randomized to receive either the combination of PEG IFN alpha 2a and lamivudine or PEG IFN alpha 2a with placebo, or lamivudine alone.³ At the end of treatment, mean decrease in HBV DNA was 5.0, 4.1, and 4.2 log copies per mL; 49%, 38%, and 73% had normal ALT; and 87%, 63%, and 73% had undetectable HBV DNA. Six months post-treatment, 60%, 59%, and 44% had normal ALT; 20%, 19%, and 7% had undetectable HBV DNA; 2%, 3%, and 0% had HBs seroconversion in the combination, the PEG IFN monotherapy, and the lamivudine

monotherapy arms, respectively. Rates of resistance to lamivudine were 1% and 18% in the combination and the lamivudine monotherapy arms, respectively.

Safety

The safety profile of the combination was similar to that of the PEG IFN monotherapy, with no unexpected adverse events. The frequency of depression was lower than that observed in trials of PEG IFN in patients with chronic hepatitis C.

Conclusion

The combination of PEG IFN with lamivudine is more effective than PEG IFN monotherapy during treatment; however, there was no difference 6 months post-treatment. The combination of PEG IFN with lamivudine has a more potent antiviral effect than lamivudine monotherapy and is associated with a lower incidence of lamivudine resistance. HBs seroconversion was only observed in the patients who received PEG IFN with or without lamivudine. Further studies are needed to assess the efficacy of the combination of PEG IFN with more potent nucleoside or nucleotide analogues for a longer duration.

References

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